CLAIMS

We claim:

1. Ondansetron hydrochloride monohydrate.

2. Ondansetron hydrochloride monohydrate containing about 5% water.

3. The ondansetron hydrochloride monohydrate of claim 1 characterized by a powder X-ray diffraction pattern having a strong peak at 23.3±2 degrees two-theta.

4. The ondansetron hydrochloride monohydrate of claim 3 further characterized by peaks in the powder X-ray diffraction pattern at 6.1, 12.4, 17.0, 18.3, 19.2, 20.3, 20.9, 24.1, 25.8, 28.1 and 30.3 ±0.2 degrees two-theta.

5. A process for preparing the ondansetron hydrochloride monohydrate of claim 1 comprising the steps of:
   a) contacting crystals of ondansetron hydrochloride dihydrate with a mixture of from about 4% to about 50 % water in ethanol,
   b) separating the ethanol:water mixture, and
   c) recovering the crystals as ondansetron hydrochloride monohydrate.

6. The process of claim 5 wherein the contacting occurs at the reflux temperature of the ethanol:water mixture.

7. The process of claim 5 wherein the dihydrate and monohydrate are denominated Form A expressing that their crystal structures are the same.

8. A process for preparing ondansetron hydrochloride dihydrate Form A comprising the steps of:

a) providing crystals of the ondansetron hydrochloride monohydrate of claim 1,

b) hydrating the crystals under an atmosphere of 50% relative humidity or greater, and

c) collecting the hydrated crystals containing about 10% water of crystallization.

9. Ondansetron hydrochloride Form A containing between about 5% water and 10% water.

10. A process for preparing the ondansetron hydrochloride Form A of claim 9, comprising the steps of:

a) suspending ondansetron free base in a liquid medium selected from the group consisting of absolute ethanol, a mixture of ethanol and isopropanol, and chloroform,

b) dissolving the free base by adding anhydrous HCl to the suspension,

c) crystallizing ondansetron hydrochloride from the liquid medium, and

d) separating the crystals from the liquid medium.

11. The process of claim 10 wherein the liquid medium is absolute ethanol.

12. The process of claim 10 wherein the HCl is added in an amount of 1 ±0.1 equivalent with respect to the ondansetron free base.

13. The process of claim 10 wherein the anhydrous HCl is added as a gas.

14. The process of claim 10 wherein the anhydrous HCl is added in solution in an inert organic solvent.

15. The process of claim 10 wherein the absolute ethanol is heated to hasten the

dissolution of the ondansetron free base.

16. A process for preparing the ondansetron hydrochloride Form A of claim 9 comprising the steps of:

a) dehydrating crystals of ondansetron hydrochloride dihydrate by contacting with a liquid medium selected from the group consisting of ethanol, mixtures of ethanol and water, toluene and mixtures of ethanol and toluene,

b) separating the liquid medium from the crystals, and

c) collecting the crystals..

17. The process of claim 16 wherein the crystals are mechanically agitated during dehydration.

18. The process of claim 17 wherein the mechanical agitation is sonication.

19. Anhydrous ondansetron hydrochloride.

20. Anhydrous ondansetron hydrochloride Form B

21. Ondansetron hydrochloride Form B characterized by powder X-ray diffraction peaks at 10.5, 11.9, 13.0, 13.5, and 15.1 ±0.2 degrees two-theta.

22. Ondansetron hydrochloride Form B characterized by powder X-ray diffraction peaks at 10.5, 11.9, 10.5, 13.0, 13.5, 15.1, 20.9, 22.7, 24.0, and 25.7 ±0.2 degrees two-theta.

23. A pharmaceutical composition comprising the ondansetron hydrochloride of any of claims 1 through 22 and a pharmaceutically acceptable carrier.

24. A method for treating nausea and/or vomiting with the pharmaceutical composition of claim 23.

25. A process for preparing the ondansetron hydrochloride of any of claims 19 through 22 by treating ondansetron hydrochloride with a dry alcohol.

26. The process of claim 25 wherein the solvent is absolute ethanol.

27. The process of claim 25 wherein ondansetron hydrochloride that is treated with dry alcohol is Form A.

28. The process of claim 25 wherein the treatment is carried out at about 20°C.

29. The process of claim 28 wherein ondansetron hydrochloride that is treated with dry alcohol is Form A.

30. The process of claim 25 wherein the alcohol is ethanol, isopropanol, 1-butanol or a mixture of thereof.

31. The process of claim 30 wherein ondansetron hydrochloride that is treated with dry alcohol is Form A.

32. A process of preparing the ondansetron hydrochloride of any of claims 19 through 22 by treating ondansetron HCl in a dry organic solvent.

33. The process of claim 32 wherein the solvent is absolute ethanol.

34. The process of claim 32 wherein ondansetron hydrochloride that is treated with dry alcohol is Form A.

35. The process of claim 32 wherein the solvent is a ketone.

36. The process of claim 35 wherein ondansetron hydrochloride that is treated with dry alcohol is Form A.

37. The process of claim 32 wherein the treatment is carried out at about 20°C.

38. The process of claim 37 wherein ondansetron hydrochloride that is treated with dry alcohol is Form A.

39. Ondansetron hydrochloride Form B having a particle size below about 300 microns.

40. A pharmaceutical composition comprising the ondansetron hydrochloride Form B of claim 39 and a pharmaceutically acceptable carrier.

41. Ondansetron hydrochloride Form B having a particle size below about 200 microns.

42. A pharmaceutical composition comprising the ondansetron hydrochloride Form B of claim 41 and a pharmaceutically acceptable carrier.

43. Ondansetron hydrochloride Form B having a particle size below about 40 microns.

44. A pharmaceutical composition comprising the ondansetron hydrochloride Form B of claim 43 and a pharmaceutically acceptable carrier.

45. Anhydrous ondansetron hydrochloride Form B with a water content up to about 2%.

46. A process for preparation of ondansetron hydrochloride Form B comprising reacting HCl gas with a toluene solution of ondansetron base.

47. The process of claim 46 wherein the ondansetron hydrochloride is dissolved at the reflux temperature of toluene.

48. The process of claim 46 wherein gaseous hydrochloride is bubbled into the toluene solution of ondansetron.

49. Ondansetron hydrochloride Form C and hydrates thereof, characterized by powder X-ray diffraction peaks at 6.3 and 24.4±0.2 degrees two-theta and other peaks at 9.2, 10.2, 13.1 and 16.9±0.2 degrees two-theta.

50. Ondansetron hydrochloride Form C and hydrates thereof, characterized by powder X-ray diffraction peaks at 6.3, 9.2, 10.2, 13.1, 16.9 and 24.4±0.2 degrees two-theta.

51. A process for preparation of the product of claim 49 or 50 which comprises the steps of:

a) dissolving ondansetron base in ethanol,

b) adding an ethanolic solution of hydrochloride,

c) filtering, and

d) evaporating the mother liquor.

52. Ondansetron hydrochloride Form D and hydrates thereof, characterized by powder X-ray diffraction peaks at 8.3, 14.0, 14.8 and 25.5±0.2 degrees two-theta.

53. A process for preparing the ondansetron hydrochloride Form D and hydrates

thereof of claim 52 comprising the steps of:

a) melting ondansetron hydrochloride in the presence of xylene; and

b) adding the melt to ethanol.

54. The process of claim 53 wherein ondansetron hydrochloride Form A is melted in the presence of xylene.

55. The process of claim 53 wherein ethanol is at a temperature of from about -15°C to about room temperature.

56. The process of claim 55 wherein the ethanol is at a temperature of about -10°C.

57. Ondansetron hydrochloride Form E and hydrates thereof, characterized by a strong powder X-ray diffraction peak at 7.4 degrees two-theta and other typical peaks at 6.3, 10.5, 11.2, 12.3, 13.0, 14.5, 15.9, 1 20.1, 20.8, 24.5, 26.2 and 27.2±0.2 degrees two-theta.

58. Ondansetron hydrochloride Form E and hydrates thereof, characterized by a strong powder X-ray diffraction peak at 7.4 degrees two-theta and other typical peaks at 6.3, 10.5, 11.2, 12.3, 13.0, 14.5, 15.9, 1 20.1, 20.8, 24.5, 26.2 and 27.2±0.2 degrees two-theta.

59. A process for preparation of the product of claim 57 or 58 which comprises the step of treating ondansetron hydrochloride in isopropanol.

60. The process of claim 59 wherein the ondansetron hydrochloride is Form A.

61. The process of claim 59 wherein the temperature of the isopropanol is from about room temperature to about reflux temperature.

62. Ondansetron hydrochloride isopropanolate.

63. Ondansetron hydrochloride Form E isopropanolate.

64. Ondansetron hydrochloride Form E mono-isopropanolate.

65. Ondansetron hydrochloride Form E hemi-isopropanolate.

66. Ondansetron hydrochloride Form E having a water content of up to about 10%.

67. Ondansetron hydrochloride Form H and hydrates thereof, characterized by powder X-ray diffraction peaks at 7.8, 14.0, 14.8 , 24.7 and 25.6±0.2 degrees two-theta.

68. A process for preparing the ondansetron hydrochloride Form H of claim 67 which comprises the steps of:

a) suspension of ondansetron base in absolute ethanol;

b) adding an ethanol solution of hydrochloric acid;

c) precipitating with the addition of ether; and

d) isolating the product.

69. The process of claim 68 wherein the ether is methyl tert-butyl ether or diethyl ether.

70. The process of claim 68 wherein the ether is dry.

71. A pharmaceutical composition comprising the ondansetron hydrochloride of any of claims 49, 50, 52, 57, 58 and 62 - 67 and a pharmaceutically acceptable

carrier.

72. Ondansetrion hydrochloride methanolate.

73. Ondansetron hydrochloride methanolate Form I.

74. Ondansetron hydrochloride Form I and hydrates thereof, characterized by a strong XRD peak at 25.0±0.2 degrees two-theta and other XRD peaks at 8.2, 9.3, 9.9, 11.1 and 24.9±0.2 degrees.

75. Ondansetron hydrochloride Form I and hydrates thereof, characterized by a strong XRD peak at 25.0±0.2 degrees two-theta and other XRD peaks at 8.2, 9.3, 9.9, 11.1, 13.9, 16.0, 17.0, 21.0, 22.6, 25.8, 27.3 and 28.0 ±0.2 degrees.

76. Ondansetron hydrochloride Form I and hydrates thereof, characterized by a strong XRD peak at 25.0±0.2 degrees two-theta and other XRD peaks at 6.9, 8.2, 8.7, 9.1, 9.3, 9.9, 11.1, 11.6, 13.8, 16.1, 16.9, 17.9, 21.1, 22.7, 25.7, 26.6, 27.4 and 27.9 ±0.2 degrees.

77. A process for crystallizing ondansetron hydrochloride Form I comprising exposing ondansetron hydrochloride to methanol vapor.

78. The process of claim 77 wherein the exposure is for a period of about three weeks or less.

79. The process of claim 77 wherein the exposure is at room temperature.

80. The process of claim 77 wherein ondansetron hydrochloride Form A is exposed to methanol vapor.

81. The process of claim 77 wherein ondansetron hydrochloride Form B is exposed to methanol vapor.

82. A process for preparing anhydrous ondansetron hydrochloride Form B comprising the steps of:

a) dissolving ondansetron base in absolute ethanol;

b) adding an ethanol/hydrochloric acid solution; and

c) filtering.

83. The process of claim 82 wherein the ethanol is substantially dry.

84. The process of claim 82 wherein the ondansetron base and the ethanol/hydrochloric acid solution are mixed at room temperature.

85. The process of claim 82 wherein the mixture of ondansetron base is heated to reflux temperature.

86. The process of claim 82 wherein the ondansetron base and the ethanol/hydrochloric acid solution are mixed for a period of about 30 to about 70 hours at room temperature.

87. Ondansetron hydrochloride with a particle size distribution of 100% particle size below about 100 microns.

88. Ondansetron hydrochloride with particle size distribution of 100% particle size below about 50 microns.

89. A pharmaceutical composition comprising ondansetron with a particle size distribution of 100% particle size below about 200 microns and a pharmaceutically acceptable carrier.

90. A pharmaceutical composition comprising ondansetron with a particle size distribution of 100% particle size below about 100 microns and a pharmaceutically acceptable carrier.

91. A pharmaceutical composition comprising ondansetron with particle size distribution of 100% particle size below about 50 microns and a pharmaceutically acceptable carrier.

92. A method for treating nausea and/or vomiting comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical composition of claim 91.

93. A pharmaceutical composition containing ondansetron hydrochloride Form I and a pharmaceutically acceptable carrier.